

U.S. Serial No. 09/709,043
Filed: November 10, 2000
AMENDMENT AND RESPONSE TO OFFICE ACTION

Remarks

Amendments to the Claims

The undersigned greatly appreciates the examiner's careful review of the pending claims. The claims have been amended to correct antecedent basis, as discussed.

Priority Claim

As discussed at the interview, the priority of this application was amended January 22, 2003, to claim priority to U.S.S.N. 09/699,003 filed October 26, 2000, which is a continuation of U.S.S.N. 09/316,226 filed May 21, 1999, now U.S. Patent No. 6,231,536, which claims priority to U.S.S.N. 09/083,307 filed May 22, 1998, and to U.S.S.N. 60/164,695 filed November 10, 1999.

Rejection under 35 U.S.C. 103

Claims 1-3, 6, 8-11, and 17-22 were rejected under 35 U.S.C. 103(a) as obvious over Selinsky, et al., Immunology 94(1):88-93 (1998) in combination with Van Zee, et al., Proc. Natl. Acad. Sci. USA (1992) in view of U.S. Patent No. 4,708,713 to Lentz and U.S. Patent No. 6,017,527. Claim 5 was rejected under 35 U.S.C. 103 over Selinsky, Van Zee, Lentz, Maraskovsky and Feinman, et al., J. Immunol. 138:635 (1987). Claim 10 was rejected under 35 U.S.C. 103 as obvious over Selinsky, Van Zee, Lentz, Maraskovsky, and Goodman. It is understood these rejections are being withdrawn in view of the Declaration under 35 U.S.C. 131 submitted in U.S. Patent No. 6,379,708 to Howell, et al.

Lentz

Lentz describes removal of a large number of proteins using a filter. The only selectivity is by virtue of the molecular weight cutoff of the filter, which is approximately

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200,000. ALL proteins in the plasma with the possible exception of some IgM will pass through a filter with a cutoff of 200,000. Therefore the limitations of claims 1-5, 8, 12 and 20 are not met.

Assuming the examiner meant to make a rejection under 35 U.S.C. 103, Selinsky does not make up for the deficiency of Lentz. Lentz teaches away from the selective removal of soluble cytokine receptor molecules. **Lentz states that the immune inhibitor which is being removed is believed to be a high molecular weight compound, not a soluble cytokine inhibitor such as soluble TNF receptor, which has a significantly lower molecular weight. Moreover, Lentz clearly does not know what the inhibitor(s) are, indicating that there are more than one inhibitor. In summary, Lentz teaches one of ordinary skill in the art that (1) the inhibitors are high molecular weight proteins and (2) there are more than one inhibitors involved in immunosuppression of the anti-tumor response.**

Selinsky

Selinsky describes an experiment to correlate the levels of soluble tissue necrosis factor receptor ("sTNFR") with tumor burden. This in no way makes obvious the removal of sTNFR to treat tumors or other disorders. The standard under 35 U.S.C. 103 is whether the prior art leads one of ordinary skill in the art to combine the prior art as applicant has done, *with a reasonable expectation of success*.

The prior art at the time this application was filed in May 1998, was that there were a number of tumor markers that correlated with tumor burden. The most well known include the prostate specific antigen ("PSA") and carcinoembryonic antigen ("CEA"). Studies had been conducted to remove both PSA and CEA, with the hope of

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decreasing tumor burden. Neither had been effective. Therefore, one skilled in the art would have had no expectation of success that removal of a soluble cytokine receptor such as sTNFR would be effective.

Indeed, this is clearly the opinion shared by the authors of the paper, as demonstrated by the previously submitted copy of the Declaration under 37 C.F.R. 1.132 filed in U.S.S.N. 09/444,144, which subsequently issued as U.S. Patent No. 6,379,708 to Howell, et al. The examiner's attention is drawn to pages 2-3 of the declaration, discussing first the Lentz patent and then the Selinsky paper. As the authors of the Selinsky paper noted:

"It is submitted that, although the statement in Selinsky et al. may cause one of skill in the art to consider how to antagonize or remove sTNFR1 *in situ*, such a statement is merely an invitation to experimentation and opens the door for one of skill in the art to consider a wide range of possible approaches. Indeed, Selinsky et al. provides absolutely no guidance as to how one of skill in the art would go about such a task, but rather generally state that the "therapeutic utility of manipulating sTNFR1 levels *in vitro* has been demonstrated" and that "sTNFR1 effectively inhibits immune responses *in vivo* and ...its modulation is a legitimate therapeutic avenue." It is submitted that one of skill in the art, when presented with an invitation to manipulate the effects of a soluble protein, would look to a variety of conventional approaches to remove or manipulate the effects of that soluble protein *in vivo*, because such approaches are the most clinically desirable means of treating a patient."

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Van Zee

Van Zee merely reports that soluble receptors for TNF are present during inflammation and that excessive TNF present during the inflammation can be neutralized by binding to soluble TNF receptors.

This reference therefore *teaches away from what is claimed*. Van Zee teaches that one can decrease inflammation using soluble TNFR to TNF. Applicant claims a method of *increasing inflammation and the immune response against tumors by removing sTNFR*.

Maraskovsky

Maraskovsky does teach that one can use an antibody column to remove materials from the blood. There is no teaching that it can be used to remove cytokine inhibitors to kill tumor cells.

For the same reasons that the examiner allowed the claims in the Howell patent over the combination of Lentz and Selinsky, so are the claims in this application allowable over Selinsky, Van Zee, Lentz, and Maraskovsky.

Feinman

Feinman does not make up for the deficiencies of the references discussed above. Feinman is not drawn to an *in vivo* situation, nor to treatment of tumor cells. Numerous studies have failed to demonstrate that interferon is useful in treating cancer.

Goodman

The examiner's characterization of the claimed method is inaccurate. The claims do not recite treating whole blood, but encompass treating whole blood or plasma. As described in the application, the blood is collected then separated into red cells and

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plasma, the plasma passed over the immunoaffinity column, then the red cells recombined with the plasma and the blood returned to the patient.

Goodman discloses making humanized antibodies. This does not make up for the deficiencies of the other references, however. Moreover, there is no motivation to use humanized antibodies, since these are immobilized, not administered to a patient.

Proposed Interference

Claims 17-22 have been added, which essentially correspond to U.S. Patent No. 6,379,708 to Howell, et al. This application claims priority to U.S.S.N. 09/083,307 filed May 22, 1998, before the earliest filing date of the Howell patent.

A proposed count is:

A method of enhancing an immune response in a patient comprising:

- a. obtaining whole blood from the patient;
- b. separating out the plasma;
- c. contacting the plasma with antibody specifically binding to a targeted immune system inhibitor;
- d. removing the inhibitor bound to the antibody from the plasma; and
- e. returning the antibody-contacted plasma to the patient.

The basis for the claims is indicated in the claims as shown below in bold. The basis as found in Applicant's May 22, 1998, application is also shown below in italics.

17. A method of enhancing an immune response in a patient (**page 1, lines 6-7**)

comprising:

- a. obtaining whole blood from the patient (**page 18, lines 4-8**); (*page 6*)
- b. separating out the plasma. (**page 18, lines 7-8**); (*page 6*)

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- c. contacting the plasma with antibody specifically binding to a targeted immune system inhibitor (**page 18, lines 8-11; page 6, lines 1-7**); (*page 11, lines 23-26*)
- d. removing the inhibitor bound to the antibody from the plasma (**page 18, line 8-11**); (*page 11, lines 23-26*) and
- e. returning the antibody-contacted plasma to the patient. (**page 18, lines 11-15**). (*page 7*)
18. The method of claim 17, wherein the antibody is immobilized in a solid support or membrane. (**page 9, lines 1-5**) (*page 11, lines 27-28*)
19. The method of claim 17, wherein the antibody is recombinant or a binding fragment. (**page 6, lines 18-20**). (*page 11, lines 24-26*)
20. The method of claim 17, wherein the antibody is a mixture of antibodies immunoreactive with the targeted immune system inhibitor. (**page 6, line 27**) (*page 11, lines 22-29*)
21. The method of claim 17, wherein the patient is human. (**page 6, line 26**). (*examples*)
22. The method of claim 17 wherein the targeted immune system inhibitor is selected from the group consisting of soluble receptors for tumor necrosis factors alpha and beta. (*page 11, lines 22-29*)

Double Patenting Rejection

As described by Chisum, "[d]ouble patenting is concerned with attempts to claim the same or related subject matter twice. Thus, the standard for comparison for the second patent is what was claimed in the first patent, not what was disclosed in the specification of the first patent." *Chisum*, 3:9.03[1][a]. "[A]n obviousness-type double patenting analysis entails two-steps." Eli Lilly & Co. v. Barr Laboratories, Inc., 251 F.3d 955, 58 U.S.P.Q.2d 1865 (Fed. Cir. 2001). First, one compares the later claim on the

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earlier claim to determine the differences. Second, one determines whether the differences in subject matter between the two claims demonstrates that the claims are patentably distinct. *Id.*, see M.P.E.P. § 804, III (The rejection "must rely on a comparison **with the claims** in an issued or to be issued patent,...") (emphasis added). The Examiner failed to properly apply this standard of analysis.

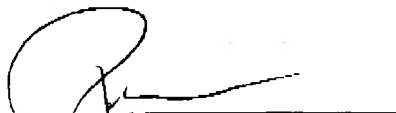
The claims in U.S. Patent No. 6,231,536 were interpreted by the examiner as requiring removal of the soluble tissue necrosis factor receptor using a molecular weight exclusion. There is nothing in such an interpretation that would make obvious the method as currently claimed.

Since the 6,231,536 patent has already issued, and the term of the present application is dependent on declaration of an interference, and ultimately award of priority to the applicant (patent term being adjusted to compensate for the time lost in an interference, which can be many years), it is not necessary to resolve this issue at this time. It is more properly an issue that can be resolved by filing of a Terminal Disclaimer, if still deemed appropriate, once the interference is resolved.

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Provisional allowance of claims 1-3, 5, 6, 8-11 and 17-22 and declaration of an
interference with U.S. patent No. 6,379,708 is respectfully requested.

Respectfully submitted,



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